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<b>(21) International Application Number:</b> PCT/IB98/01982 <b>(22) International Filing Date:</b> 7 October 1998 (07.10.98) <b>(71) Applicant:</b> ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). <b>(71)(72) Applicant and Inventor:</b> KIDNEY, David, J. [IE/US]; 250 Davenport Way, Palo Alto, CA 94306 (US). <b>(72) Inventors:</b> GUITTARD, George, V.; 22434 St. Andrews Avenue, Cupertino, CA 95014 (US). JAO, Francisco; 5260 Arezzo Drive, San Jose, CA 95138 (US). MARKS, Susan, M.; 1815 Newport Avenue, San Jose, CA 95125 (US). GUMUCIO, Fernando; 3063 Forbes, Santa Clara, CA 95051 (US). <b>(74) Agents:</b> STEBBING, Peter, John, Hunter et al.; Ablett & Stebbing, Caparo House, 101-103 Baker Street, London W1M 1FD (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> CONTROLLED RELEASE DOSAGE FORM COMPRISING OXYBUTYNIN  <b>(57) Abstract</b> <p>The present invention relates to a desethyl metabolite of oxybutynin and its reduction in the circulating plasma. Specifically the invention relates to a controlled release dosage form comprising oxybutynin or a pharmaceutically acceptable biologically active salt thereof adapted to release oxybutynin or its salt at a biological rate over time to an environment of use wherein the oxybutynin or active salt thereof is adapted to be partially converted to its desethylmetabolite in the environment of use and in that the rate of release of oxybutynin or salt thereof from the dosage form is adapted to provide a controlled release of up to 30 hours to provide a higher oxybutynin/desethyl metabolite ratio than 0.18:1 or such that the plasma levels of the metabolite do not exceed 350 ng.h/ml in use.</p>		

## CONTROLLED RELEASE DOSAGE FORM COMPRISING OXYBUTYNIN

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This invention pertains to a novel dosage form comprising oxybutynin and to the manufacture of a sustained release dosage form for managing the concentration of oxybutynin and its metabolite.

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**BACKGROUND OF THE INVENTION**

15 Many people are affected by urinary incontinence. Incontinence is particularly common in the elderly; urinary incontinence is present in approximately fifty percent of nursing home patients, and urinary incontinence is a well known urologic problem in women. It will affect nearly all women in some form during their lifetime, and it is of significant social concern to all  
20 humans who experience it.

Urinary incontinence arises from the anatomy and the physiology of the urinary tract, which is composed of a bladder and a sphincter. Anatomically, the bladder consists of the bladder musculature, also known as detrusor, and the trigone. The sphincter includes the bladder neck and the  
25 proximal urethra. The detrusor muscle is innervated by the pelvic nerve through the parasympathetic nervous system, and the bladder neck and proximal urethra are innervated by the sympathetic nervous system.

The major functions of the bladder are the storage and expulsion of urine. The bladder is responsible for accommodating increasing volumes of urine at low pressures. Normally, the bladder remains closed during bladder  
30 filling and continence is maintained as long as the bladder neck and urethral

pressure exceeds intravesical pressure. Voluntary voiding occurs when intravesical pressure exceeds bladder neck and urethral pressure, and involuntary voiding occurs when the intravesical pressure exceeds the bladder neck and urethral pressure.

5        Involuntary incontinence, also known as urge incontinence, occurs with a loss of a large volume of urine accompanied by symptoms of urgency, frequency and nocturia caused by an unstable bladder or detrusor instability. The patient may lose urine with a change in position or with auditory stimulation. The loss of small volumes of urine usually occurs because of  
10       bladder overdistension by a large amount of residual urine referred to as overflow incontinence.

         The management of incontinence consists in administering a smooth muscle relaxant, such as oxybutynin, which acts directly on the smooth muscle at the site distal to the cholinergic receptor. The usual dose in the  
15       pharmacologic management is repeated doses from two-to-four times a day for oxybutynin. This is difficult to achieve as it requires rigid compliance and it is cost ineffective. Also, oxybutynin is adversely affected by light and it needs protection from air, which properties do not lend the drug to formulation into a dosage form that can administer oxybutynin at a controlled and known rate  
20       per unit time to produce the intended therapy.

         In light of the above presentation it will be appreciated by those versed in the medical and pharmaceutical dispensing arts to which this invention pertains that a pressing need exists for a dosage form and for a therapeutic composition that can deliver the valuable drug oxybutynin in a controlled,  
25       extended dose to a patient in clinical need of incontinence management.

The need exists additionally for a sustained-release dosage form comprising a therapeutic composition that can deliver a therapeutic dose of oxybutynin for its intended effect, for avoiding an overdose, and for lessening the side effects that can accompany the drug. It will be appreciated further by those skilled in the dispensing art that if such a novel and unique dosage form are made available that can administer oxybutynin in a beneficial dose over time and simultaneously provide oxybutynin while lessening the incidence of both over and under dose, the dosage form would represent an advance and a valuable contribution to the medical arts.

One of the problems associate with oxybutynin administration is that it is converted at least in part to its desethyl metabolite (Desoxy) in the plasma. We have found that if the Desoxy metabolite levels in the plasma rise too high, unwanted side effects such as anticholinergic effects occur. We have now found however that if the rate at which oxybutynin is delivered to the plasma from a controlled rate device is controlled to avoid peaks in delivery rate, the circulating desoxy metabolite levels are reduced and side effects are materially reduced at the same time.

Thus we have found that if the controlled rate device comprising oxybutynin delivers the oxybutynin to an environment use at a rate which gives an oxybutynin/desoxy metabolite ratio higher than 0.18:1 and/or the plasma levels of the desoxy metabolite do not exceed 350 ng.h/ml, side effects are significantly reduced.

According to a first feature of the invention, there is provided a controlled release dosage form comprising

oxybutynin or a pharmaceutically acceptable biologically active salt thereof adapted to release oxybutynin or its salt at a biologically effective rate over time to an environment of use. The invention is characterized in this aspect in that the oxybutynin or active salt is adapted to be partially converted to desethyl metabolite in the environment of use and in that the rate of release of oxybutynin or salt thereof from the dosage form is adapted to provide a controlled release up to 30 hours to provide a higher oxybutynin/desethyl metabolite ratio than 0.18:1.

In a second form of the invention there is provided a controlled release dosage form comprising oxybutynin or a pharmaceutically acceptable biologically active salt thereof adapted to release the oxybutynin or salt thereof at a biologically effective rate over time to an environment of use. The invention in this aspect is characterized in that the oxybutynin or salt thereof is adapted to be partially converted to a desethyl metabolite in the environment of use and in that the rate of discharge of the oxybutynin or salt thereof from the dosage form is adapted to be controlled so that the plasma levels of the desethyl metabolite do not exceed 350 ng.h/ml. The dosage form may be adapted to reduce peak levels of the metabolite to 300 ng. h/ml or even 250 or 200 ng.h/ml.

Accordingly, in view of the above presentation it is an immediate object of this invention to provide a dosage form for delivering oxybutynin in a rate-controlled dose,

and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a pharmacologic composition comprising oxybutynin, its  
5 racemate, its R-enantiomer and its S-enantiomer, administrable to a human, for lessening the incidence of incontinence.

Another object of the present invention is to provide a sustained release dosage form that administers oxybutynin  
10 at a controlled rate over twenty-four or even 30 hours for its therapeutic benefit accompanied by a lessening of unwanted side effects.

Another object of the present invention is to provide a dosage form adapted for the oral administration of  
15  $\alpha$ -cyclohexyl- $\alpha$ -hydroxy-benzeneacetic acid-4(diethylamino)-2-butynyl ester salt in a first composition in contacting, layered arrangement with a second, force-generating composition that operates in combination for the administration of the beneficial ester salt.

20 Another object of the invention is to provide a dosage form for administering oxybutynin in a sustained-release profile to lessen side effects.

The invention thus pertains to a dosage form for the above therapeutic compositions adapted to deliver  
25 oxybutynin orally to a warm-blooded animal, including a human patient, in need of oxybutynin therapy. The dosage forms of the invention may be administered orally to a patient for oxybutynin therapy. The administration may comprise: (a) admitting orally into the patient a dosage  
30 form comprising (b) a semipermeable wall that surrounds (c) a therapeutic composition comprising (a) oxybutynin. In

use within the body, the dosage form imbibes fluid through the wall into the dosage form in response to the concentration gradient across the semipermeable wall. The therapeutic composition in the dosage form develops osmotic energy that causes the therapeutic composition to be administered through the exit (d) from the dosage form over a prolonged period of time up to 24 hours (or even in some cases up to 30 hours) to provide controlled and sustained oxybutynin therapy. The dosage form of the invention may be used by (a) admitting into the warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of oxybutynin ; (2) an oxybutynin drug layer in the compartment comprising oxybutynin ; (3) a hydrogel push layer in the compartment comprising an osmotic formulation for imbibing and absorbing fluid for expanding in size for pushing the oxybutynin composition from the delivery device; and (4) at least one passageway in the wall for releasing the oxybutynin; (B) imbibing fluid through the semipermeable wall at a fluid imbibing rate determined by the permeability of the semipermeable wall and the osmotic pressure across the semipermeable wall causing the push layer to expand; and (C) delivering the therapeutically active oxybutynin from the delivery device through the exit passageway to a warm-blooded animal over a prolonged period of time up to 24 or even 30 hours. The oxybutynin administered by the dosage form of the invention is in the therapeutic range that avoids a toxic dose and avoids an ineffective dose for antispasmodic therapy. The oxybutynin

may thus be administered to patients with uninhibited neurogenic and reflex neurogenic bladder for increased vessel capacity which diminishes the frequency of uninhibited contractions of the detrusor muscle and delays the desire to void. The dosage form is indicated for the relief of symptoms associated with voiding such as urgency, urge incontinence, frequency, nocturia and incontinence in patients in neurogenic bladder.

Other objects, features and advantages of this invention will be more apparent to those versed in the delivery arts from the following detailed specification, taken in conjunction with the accompanying claims.

#### BRIEF DESCRIPTION OF DRAWING FIGURES

Figure 1 illustrates the cumulative amount of the dose released in percent for a dosage form provided by the invention.

Figure 2 illustrates the average release rate in percent per hour for a dosage form provided by the invention.

#### DETAILED DISCLOSURE OF SPECIFICATION

In one aspect, the dosage form of the invention contains a therapeutic composition comprising 240 ng to 650 mg (nanogram to milligrams) of oxybutynin or an oxybutynin therapeutically acceptable salt. The pharmaceutically acceptable salt is selected from the group consisting of acetate, bitartrate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, hydrobromide, hydrochloride, lactate, malate, maleate, mandelate, mesylate, methylnitrate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tannate and tartrate. The



drug oxybutynin can be present as the racemate, as the R-enantiomer or as the S-enantiomer. The dosage form may further contain 20 mg to 250 mg of a hydrogel, such as 20 mg to 250 mg of a polyalkylene oxide of 75,000 to 600,000 weight-average molecular weight. Representative polyalkylenes are a polyethylene oxide of 100,000 weight-average molecular weight, of 200,000 weight average molecular weight or a polyethylene oxide of 300,000 weight-average molecular weight. The dosage form may also  
10 comprise 1 mg to 50 mg of a hydroxypropylalkylcellulose of 9,000 to 150,000 average-number molecular weight selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose; 1 mg to 40 mg of an osmotic solute selected from the  
15 osmotically effective compounds consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; and 0.01 mg to 5 mg of a lubricant, such as calcium stearate, zinc stearate, magnesium stearate, magnesium oleate, calcium palmitate, sodium  
20 suberate, potassium laureate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, and a mixture of salt of fatty, alicyclic or aromatic acid and a fatty, alicyclic or aromatic acid.

The invention provides for the therapeutic composition comprising the drug oxybutynin to be administered as the composition neat, that is,  
25 oxybutynin alone, for increasing the urinary bladder capacity, for diminishing the frequency of uninhibited contractions of the detrusor muscles and its accompanying delay of the desire to void. The invention provides for the therapeutic oxybutynin composition to be surrounded by a wall comprising a semipermeable composition with an exit for delivering the therapeutic  
30 composition to a human patient in need of oxybutynin therapy. The invention provides, in an additional embodiment, the therapeutic composition

comprising oxybutynin as a therapeutic layer in layered, contacting arrangement with a hydrogel composition manufactured as a layer that supports the therapeutic composition to yield a bilayered matrix. The hydrogel layer may comprise 40 mg to 250 mg of a hydrogel, such as a member selected from the group consisting of 40 mg to 250 mg of a polyalkylene oxide of 1,000,000 to 8,000,000 weight-average molecular weight which are selected from the group consisting of polyethylene oxide and polypropylene oxide; or 40 mg to 250 mg of an alkali carboxymethylcellulose of 10,000 to 6,000,000 weight-average molecular weight such as sodium carboxymethylcellulose or potassium carboxymethylcellulose; or 0.1 mg to 250 mg of a hydroxyalkylcellulose of 7,500 to 4,500,000 weight-average molecular weight, represented by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, and hydroxypentylcellulose; 1 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; 0 to 5 mg of a colorant, such as ferric oxide; 0.1 mg to 30 mg of a hydroxypropylalkylcellulose of 9,000 to 225,000 average-number molecular weight, selected from the group consisting of hydroxypropylethylcellulose, hydroxypropypentylcellulose, hydroxypropylmethylcellulose, and hydropropylbutylcellulose; 0.00 to 1.5 mg of an antioxidant selected from the group consisting of ascorbic acid, butylated hydroxyanisole, butylatedhydroxyquinone, butylhydroxyanisol, hydroxycomarin, butylated hydroxytoluene, cephalin, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propylhydroxybenzoate, trihydroxybutylrophenone, dimethylphenol, di-tert-butylphenol, vitamin E, lecithin and ethanolamine; and 0.1 mg to 7 mg of a lubricant selected from the group consisting of calcium stearate,

magnesium stearate, zinc stearate, magnesium oleate, calcium palmitate, sodium suberate, potassium laureate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid, and a fatty, alicyclic or aromatic  
5 acid.

10       The invention also provides for a dosage form as a therapeutic bilayer comprising an oxybutynin layer, and an osmopolymer hydrogel layer to be administered as the bilayer per se; that is, as the bilayer for increasing the urinary bladder capacity, for diminishing the frequency of  
15 uninhibited

contractions of the detrusor muscles and its accompanying delay of the desire to void. The invention provides additionally for the

compositional bilayer to be surrounded by a wall comprising a semipermeable composition with an exit for delivering the therapeutic composition to a human patient in need of oxybutynin therapy. The invention  
5 also provides for a subcoat to surround the therapeutic composition or to surround the bilayer, which subcoat in either embodiment is surrounded by a outer semipermeable wall.

The invention provides a dosage form for the delivery of the  
10 therapeutic composition comprising oxybutynin. The dosage form comprises up to 650 mg, and in one manufacture 240 ng to 650 mg of oxybutynin or its salt. The dosage form can provide a sustained release at a controlled rate up to 25 mg, and in one controlled release rate 24 ng to 25 mg of oxybutynin or  
15 its salt up to 30 hours. The dosage form comprises a wall, which wall surrounds an internal lumen or compartment. The wall comprises a semipermeable composition that is permeable to the passage of fluid and impermeable to the passage of oxybutynin. The wall is nontoxic and it comprises a polymer selected from the group consisting of a cellulose  
20 acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises 75 wt% (weight percent) to 100 wt% of the cellulosic wall-forming polymer; or, the wall can comprise additionally 0.01 wt% to 10 wt% of polyethylene glycol, or 1 wt% to 25 wt% of a cellulose, either selected from the group consisting of  
25 hydroxypropylcellulose or hydroxypropylalkylcellulose such as hydroxypropylmethylcellulose. The total weight percent of all components comprising the wall is equal to 100 wt%. The internal compartment comprises the therapeutic oxybutynin composition in layered position with an expandable hydrogel composition. The expandable hydrogel composition in the compartment increases in dimension by imbibing the fluid through the  
30 semipermeable wall, causing the hydrogel to imbibe the fluid, expand and

1 occupy space in the compartment, whereby the drug composition is pushed  
from the dosage form. The therapeutic layer and the expandable layer act  
together during the operation of the dosage form for the release of oxybutynin  
to a patient over time. The dosage form comprises a passageway in the wall  
5 that connects the exterior of the dosage form with the internal compartment.  
The dosage form provided by the invention delivers oxybutynin from the  
dosage form to the patient at a zero order rate of release over a period of 24  
hours.

The expression "passageway" as used herein comprises means and  
10 methods suitable for the metered release of the therapeutic drug from the  
compartment of the dosage form. The exit means comprises at least one  
passageway, including orifice, bore, aperture, pore, porous element, hollow  
fiber, capillary tube, porous overlay, or porous element that provides for the  
osmotic controlled release of oxybutynin. The passageway includes a  
15 material that erodes or is leached from the wall in a fluid environment of use  
to produce at least one dimensioned passageway. Representative materials  
suitable for forming a passageway, or a multiplicity of passageways comprise  
a leachable poly(glycolic) acid or poly(lactic) acid polymer in the wall, a  
gelatinous filament, poly(vinyl alcohol), leachable polysaccharides, salts and  
20 oxides. A pore passageway, or more than one pore passageway, can be  
formed by leaching a leachable compound, such as sorbitol, from the wall.  
The passageway possesses controlled-release dimensions, such as round,  
triangular, square and elliptical, for the metered release of oxybutynin from  
the dosage form. The dosage form can be constructed with one or more  
25 passageways in spaced apart relationship on a single surface or on more  
than one surface of the wall. The expression "fluid environment" denotes an  
aqueous or biological fluid as in a human patient, including the  
gastrointestinal tract. Passageways and equipment for forming passageways  
are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864

and 4,816,263. Passageways formed by leaching are disclosed in U.S. Patent Nos. 4,200,098 and 4,285,987.

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The wall of the dosage form can be formed by using an air suspension procedure. This procedure consists in suspending and tumbling the composition or the layers in a current of air and wall-forming composition until  
10 a wall is applied to the oxybutynin forming compartment. The air suspension procedure is well suited for independently forming the wall. The air suspension procedure is described in U.S. Patent No. 2,799,241; J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and ibid, Vol. 49, pp. 82-84 (1960). The wall can be formed with a wall-forming composition in a Wurster®  
15 air suspension coater using an organic solvent, such as acetone-water cosolvent 90:10 (wt:wt) with 2.5 wt% to 7 wt% polymer solids. An Aeromatic air suspension coater using, for example, a methylene dichloride methanol cosolvent comprising 87:13 (v:v) can be used for applying the wall. Other wall-forming techniques, such as pan coating system, wall forming  
20 compositions are deposited by successive spraying of the composition or the bilayered arrangement, accompanied by tumbling in a rotating pan. A larger volume of cosolvent can be used to reduce the concentration of polymer solids to produce a thinner wall. Finally, the wall of the coated compartments are laser or mechanically drilled, and then dried in a forced air or humidity  
25 oven for 1 to 3 days or longer to free the solvent. Generally, the walls formed by these techniques have a thickness of 2 to 20 mils (0.051 to 0.510 mm) with a preferred thickness of 2 to 6 mils (0.051 to 0.150 mm).

The dosage form of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial  
30 drug oxybutynin and other ingredients comprising a therapeutic composition

or comprising the first layer facing the exit means are blended, or they are blended then pressed, into a solid layer. The oxybutynin and other ingredients can be blended with a solvent and formed into a solid or semisolid formed by conventional methods such as ball-milling, calendaring, stirring or roll-milling and then pressed into a selected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form. The bilayer compositions possess dimensions corresponding to the internal lumen of the dosage form. Next, the oxybutynin hydrogel layer is placed in contact with the oxybutynin drug layer. The layering of the oxybutynin layer and the hydrogel layer can be fabricated by conventional press-layering techniques. Finally, the two-layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser drilled or mechanically drilled through the wall to contact the oxybutynin layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected drug surface.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique the oxybutynin and the ingredients comprising the first layer are blended using an organic or inorganic solvent, such as isopropyl alcohol-methylene dichloride 80:20 (v:v) as the granulation fluid. Other granulating fluid, such as water, isopropyl alcohol, or denatured alcohol 100% can be used for this purpose. The ingredients forming the first layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the first layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then, the latter prepared wet blend is slowly added to the oxybutynin blend with continual mixing in the blender. The granulating fluid is added until a wet blend mass is produced, which wet mass is then forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 25°C to 40°C. The dry granules are then screened

with a 16 mesh screen. Next, a lubricant is passed through an 60 mesh screen and added to the dry screened granule blend. The granulation is put into milling jars and mixed on a jar mill for 2 to 10 minutes. The first and second layer compositions are pressed into a layered tablet, for example, in a  
5 Manesty® layer press.

Another manufacturing process that can be used for providing the oxybutynin and hydrogel composition comprises blending their powdered ingredients in a fluid bed granulator. After the powdered ingredients are dry blended in the granulator, a granulating fluid, for example,  
10 poly(vinylpyrrolidone) in a solvent, such as in water, is sprayed onto the respective powders. The coated powders are then dried in a granulator. This process coats the ingredients present therein while spraying the granulating fluid. After the granules are dried, a lubricant, such as stearic acid or magnesium stearate, is blended as above into the mixture. The granules are  
15 then pressed in the manner described above. In another embodiment, when the fluid bed granulating process is used to manufacture the hydrogel layer, the antioxidant present in the polyalkylene oxide can be removed during the processing step. If antioxidant is desired it can be added to the hydrogel formulation; this can be accomplished during the fluid bed granulation  
20 described above.

The dosage form of this invention is manufactured in another embodiment by mixing the oxybutynin with composition-forming ingredients and pressing the composition into a solid layer possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to  
25 a passageway. In another embodiment, the oxybutynin and other drug composition forming ingredients and a solvent are mixed into a solid, or semi-solid, by conventional methods such as ball-milling, calendaring, stirring or roll-milling, and then pressed into a preselected, layer-forming shape. The invention provides further a method of manufacturing a sustained release  
30 dosage form adapted for managing oxybutynin and its desethylmetabolite in



plasma by incorporating an effective amount of oxybutynin or its salt in a controlled release dosage form that releases oxybutynin continuously at a controlled rate to provide a higher oxybutynin concentration and a lower desethylmetabolite concentration than provided by an immediate release dosage form dose-dumps. An immediate release dosage form dumps its drug in an hour or less.

In the manufactures as presented above, the manufacture comprising a composition or comprising a layer of a composition comprising a hydrogel osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug oxybutynin, and the two layers comprising the layers are surrounded with a semipermeable wall. The layering of the first drug oxybutynin composition and the second hydrogel osmopolymer and optional osmagent composition can be accomplished by using a conventional two-layer tablet press technique. The wall can be applied by molding, spraying or dipping the pressed shapes into wall-forming materials. Another technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layers in a current of air until the wall forming composition surrounds the layers. Manufacturing procedures are described in Modern Plastics Encyclopedia, Vol. 46, pp. 62-70 (1969); and In Pharmaceutical Sciences, by Remington, 14th Ed., pp. 1626-1979 (1970), published by Mack Publishing Co., Easton, PA. The dosage form can be manufactured by following the teaching in U.S. Patent Nos. 4,327,725; 4,612,008; 4,783,337; 4,863,456; and 4,902,514.

The dissolution of a drug indicates the drug entering into solution upon its delivery from a dosage form provided by this invention is measured by the following procedure. First, a drug receiving solution, such as, gastrointestinal fluid, hydrochloride acid, or an aqueous sodium dodecyl sulfate, 1% (w/v) (weight/volume) solution is used as the dissolution media. A dosage form prepared by this invention is placed into the dissolution media and the drug released by the dosage form into the dissolution media is sampled at a

constant time interval over the time period of dissolution. The filtered samples are assayed by a reversed high pressure liquid chromatography, or detection by UV. The concentration of the samples is measured against a standard curve containing, for example, at least five standard points.

5 Procedures for dissolution testing are reported in The United States Pharmacopoeia, The National Formulary, pg. 1791 to 1796; (1995); Pharmaceutical Sciences, by Remington, 17th Ed., pg. 653-666 (1985); and USP XXII, Dissolution Paddle Analysis, pg. 1578-1579 (1990).

10 The release rate of drug from a dosage form manufactured by this invention can be ascertained by the following procedure. The procedure comprises placing the dosage form in a solution, usually water, and taking aliquots of the release rate solution, followed by their injection into a chromatographic system to quantify the amount of drug released during specified test intervals. The drug, for example, is resolved on a column and  
15 detected by UV absorption. Quantitation is performed by linear regression analysis of peak areas from a standard curve containing at least five standard points.

The release rate procedure comprises attaching a dosage form to a plastic rod with the orifice exposed to the drug receiving solution. Then,  
20 attaching the rod to a release arm, with the arm affixed to an up/down reciprocating shaker, which operates at an amplitude of about 3 cm and 2 seconds per cycle. Then, continuously immersing the dosage form in 50 ml test tubes containing 30 ml of H<sub>2</sub>O, equilibrated in a constant temperature water bath at 37°C ± 0.5°C. Next, at the end of each interval, transfer the  
25 dosage form to the next row of new test tubes containing a receiving solution, such as water. After the release pattern is complete, remove the tubes and allow to cool to room temperature, followed by filling the calibrated tubes to the 50 ml mark with a solvent, such as acetone. The samples are mixed immediately, transferred to sample vials, followed by chromatography  
30 analysis.

Exemplary solvents suitable for manufacturing the wall, the composition layers and the dosage form include inert inorganic and organic solvents that do not adversely harm the materials, the wall, the layer, the composition and the drug wall. The solvents broadly include members  
5 selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate,  
10 methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethylacetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclo-octane, toluene, naphtha, 1,4-dioxane, tetrahydrofuran,  
15 diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

20 The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way. These examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure and  
25 the accompanying claims.

#### EXAMPLE 1

30 A therapeutic oxybutynin composition for use in the invention was prepared as follows: first, 103 grams of oxybutynin hydrochloride was

dissolved in 1200 ml (milliliters) of anhydrous ethanol. Separately, 2,280 g of polyethylene oxide of 200,000 weight-average molecular weight, 150 g of hydroxypropylmethylcellulose of 9,200 average-number molecular weight and 450 g of sodium chloride were dry blended in a conventional blender for 10 minutes to yield a homogenous blend. Next, the oxybutynin ethanol solution was added slowly to the blend, with the blender continuously blending until all the ingredients were added to the three component dry blend, with the blending continued for another 8 to 10 minutes. The blended wet composition was passed through a 16 mesh screen and dried overnight at a room temperature of 72°F (22.2°). Then, the dry granules were passed through a 20 mesh screen, 18 g of magnesium stearate was added, and all the ingredients blended again for 5 minutes. The fresh granules are ready for formulation into a therapeutic oxybutynin composition. The therapeutic composition comprises 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% of hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 15 wt% sodium chloride, and 0.6 wt% magnesium stearate. The therapeutic composition can be administered as the composition for its intended oxybutynin therapy.

## EXAMPLE 2

An osmopolymer hydrogel composition for use in the invention was prepared as follows: first 1274 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 weight-average molecular weight, 600 g of sodium chloride, and 20 g ferric oxide were separately screened through a 40 mesh screen. Then, all the screened ingredients were mixed with 100 g of hydroxypropylmethylcellulose of 11,200 average-number molecular weight to produce a homogenous blend. Next, 300 ml of denatured anhydrous alcohol was added slowly to the blend with continuous mixing for 5 minutes. Then,

1.6 g of butylated hydroxytoluene was added, followed by more blending, with 5 g of magnesium stearate added with 5 minutes of blending, to yield a homogenous blend. The freshly prepared granulation is passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 63.67 wt% polyethylene oxide of 7,500,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% ferric oxide, 5 mg hydroxypropylmethylcellulose of 11,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 mg magnesium stearate.

10

### EXAMPLE 3

An osmopolymer hydrogel composition for use in the invention was prepared as follows: first 1274 g of pharmaceutically acceptable sodium carboxymethylcellulose comprising a 5,250,000 weight-average molecular weight, 600 g of sodium chloride, and 20 g ferric oxide were separately screened through a 40 mesh screen. Then, all the screened ingredients were mixed with 100 g of hydroxypropylmethylcellulose of 11,200 average-number molecular weight and 100 g of hydroxypropylcellulose of 30,000 average-number molecular weight to produce a homogenous blend. Next, 300 ml of denatured anhydrous alcohol was added slowly to the blend with continuous mixing for 5 minutes. Then, 1.6 g of butylated hydroxytoluene was added, followed by more blending, with 5 g of magnesium stearate added with 5 minutes of blending, to yield a homogenous blend. The freshly prepared granulation was passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 58.67 wt% the sodium carboxymethylcellulose, 30 wt% sodium chloride, 1 wt% ferric oxide, 5 mg of hydroxypropylmethylcellulose, 5 mg hydroxypropylcellulose, 0.08 wt % butylated hydroxytoluene, and 0.25 mg of magnesium stearate.

30

EXAMPLE 4

1                   The therapeutic oxybutynin composition and the  
2                   osmopolymer hydrogel composition for example as shown in  
3                   Example 1 were made into a bilayer tablet as follows:  
4                   first, 147 mg of the oxybutynin composition as prepared in  
5                   Example 1 was added to a punch die set and tamped. Then, 98  
6                   mg of the hydrogel composition as prepared in Example 2 was  
7                   added and the two layers compressed under a pressure head  
8                   of 1.0 ton (1000 kg) into a 11/32 inch (0.873 cm) diameter,  
9                   contacting intimate bilayered tablet. The example was  
10                  repeated with the hydrogel composition as prepared in  
11                  Example 3 to produce the tablet comprising two layers.

EXAMPLE 5

13                  The bilayered tablet for example as described in  
14                  Example 4 was manufactured into a dosage form as follows:-  
15                  first, a semipermeable wall-forming composition was prepared comprising 95  
16                  wt% cellulose acetate having a 39.8% acetyl content and 5 wt% polyethylene  
17                  glycol having a number-average molecular weight of 3350 by dissolving the  
18                  ingredients in a cosolvent comprising acetone and water in 90:10 wt:wt  
19                  composition to make a 4% solid solution. The wall-forming composition was  
20                  sprayed onto and around the bilayered cores as prepared in Examples 2 and  
21                  3 to provide a 26.4 mg semipermeable wall.

22                  Next, the semipermeable walled, bilayered tablet was laser drilled to  
23                  provide a 20 mil (0.51 mm) orifice to contact the oxybutynin layer and the  
24                  exterior of the dosage form. The residual solvent was removed by drying for  
25                  48 hours at 50°C and 50% relative humidity. Next, the dosage forms were  
26                  dried further for 1 hour at 50°C to remove excess moisture. The dosage form  
27                  provided by this manufacture provides 3.4 wt% oxybutynin hydrochloride, 76  
28                  wt% poly thylene oxide of 200,000 weight-average molecular weight, 5 wt%  
29                  hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6  
30

wt% magnesium stearate, and 15 wt% sodium chloride in the therapeutic oxybutynin composition. The osmopolymer hydrogel push composition comprises 63.67 wt% polyethylene oxide of 7,500,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% ferric chloride, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 wt% magnesium stearate. The semipermeable wall comprises 95 wt% cellulose acetate comprising 39.8% acetyl content, and 5 wt% polyethylene glycol of 3350 number-average molecular weight. The dosage form comprises an exit passage of 20 mils (0.50 mm) and it has a mean release rate of 0.260 mg/hr for 23.8 hours. The semipermeable wall provides substantial protection from photo (light) degradation of the oxybutynin in the dosage form.

#### EXAMPLE 6

A dosage form is prepared according to the above examples, comprising a drug layer consisting of 6.67 wt% oxybutynin hydrochloride, 87.83 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5.00 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, and 0.50 wt% magnesium stearate; in layered contact with a push hydrogel layer comprising 58.75 wt% sodium carboxymethylcellulose of 6,000,000 weight-average molecular weight, 30 wt% sodium chloride, 5.00 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 1.00 wt% ferric oxide, 5.00 wt% hydroxypropylcellulose of 75,000 average-number molecular weight and 0.25 wt% magnesium stearate; which bilayered core is surrounded by a semipermeable wall comprising cellulose acetate and polyethylene glycol; and an exit port through the wall for delivering the oxybutynin at a controlled rate over thirty hours.

**EXAMPLE 7**

The dosage form according to Example 6 wherein the polyethylene oxide has a 300,000 weight-average molecular weight; the  
5 hydroxypropylcellulose is a member selected from the group consisting of 25,000, 30,000 or 40,000 average-number molecular weight; and the dosage form comprises 5 mg to 250 mg of oxybutynin pharmaceutically acceptable salt.

10

**EXAMPLE 8**

A dosage form was prepared according to the above examples wherein the dosage form of this example comprises a drug oxybutynin layer comprising 5 mg oxybutynin, 111.60 mg polyethylene oxide of 200,000  
15 weight-average molecular weight, 7.35 mg hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.88 mg magnesium stearate, 22.05 mg of sodium chloride, and 0.12mg of butylated hydroxytoluene; a hydrogel push layer comprising 62.40 mg of polyethylene oxide of 7,000,000 weight-average molecular weight, 29.40 mg of sodium chloride, 4.90 mg  
20 hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 mg of butylated hydroxytoluene, 0.98 mg of red ferric oxide, and 0.24 mg of magnesium stearate; a wall comprising cellulose acetate consisting of a 39.8% acetyl content and polyethylene glycol of 3350 number-average molecular weight in the percentage ratio of 95 wt% cellulose acetate to 5 wt%  
25 polyethylene glycol, and an exit passageway in the wall.

**EXAMPLE 9**

A dosage form was prepared according to the examples provided by  
30 this invention wherein the dosage form comprises: a drug oxybutynin layer



comprising 5.3 wt% oxybutynin, 82.37 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.25 wt% magnesium stearate, 10 wt% sodium chloride, and 0.08 wt% butylated hydroxytoluene; a push  
5 hydrogel layer comprising 63.37 wt% polyethylene oxide of 2,000,000 weight-average molecular weight, 30 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, 1 wt% black ferric oxide and 0.25 wt% magnesium stearate; a wall comprising 99 wt% cellulose acetate comprising a 39.8%  
10 acetyl content and 1 wt% polyethylene glycol of 3350 number-average molecular weight; and an exit passageway through the wall for delivering the oxybutynin to a patient.

#### **EXAMPLE 10**

15 An oxybutynin composition was prepared according to the above examples, wherein the composition comprises 10.6 wt% oxybutynin hydrochloride, 79.57 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-  
20 number molecular weight, 0.25 wt% of magnesium stearate, 7.5 wt% of sodium chloride, and 0.08 wt% butylated hydroxytoluene.

#### **EXAMPLE 11**

25 An oxybutynin composition was prepared according to the above examples wherein the composition comprises 16 wt% oxybutynin hydrochloride, 76.67 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-  
number molecular weight, 0.25% magnesium stearate, 5 wt% sodium chloride  
30 and 0.08 wt% butylated hydroxytoluene.

**EXAMPLE 12**

A hydrogel composition was prepared according to the above examples wherein the composition comprises 58.75 wt%

5 hydroxyethylcellulose of 1,300,000 molecular weight, 30 wt% sodium chloride, 10 wt% polyvinylpyrrolidone of 42,000 viscosity-average molecular weight, 1 wt% red ferric oxide, and 0.25 wt% magnesium stearate.

**EXAMPLE 13**

10

A dosage form was prepared according to the present invention wherein the dosage form comprises: a drug layer comprising 3.4 wt%

oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200  
15 average-number molecular weight, 0.6 wt% magnesium stearate, 15 wt% sodium chloride; a push hydrogel layer comprising 58.75 wt%

hydroxyethylcellulose of 1,300,000 average-number molecular weight, 30 wt% sodium chloride, 10 wt% polyvinylpyrrolidone of 42,000 viscosity-average molecular weight, 1 wt% red ferric oxide, and 0.25 wt% magnesium stearate;

20 a wall comprising 95 wt% cellulose acetate comprising a 39.8% acetyl content, and 5 wt% polyethylene glycol of 3350 number-average molecular weight, an exit orifice of 20 mil (0.50 mm); and a release rate of 0.292 mg per 1 hour for 16.9 hours.

25

**EXAMPLE 14**

A dosage form was manufactured according to the present examples wherein the dosage form comprises: a drug oxybutynin layer comprising 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200  
30

average-number molecular weight, 0.6 wt% of magnesium stearate, and 15 wt% sodium chloride; a push hydrogel layer for pushing the drug oxybutynin layer from the dosage form comprising 63.67 wt% polyethylene oxide of  
5 7,000,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% red ferric oxide, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 wt% magnesium stearate; a subcoat that surrounds the drug oxybutynin layer and push hydrogel layer wherein the subcoat comprises 95 wt% hydroxyethyl-  
10 cellulose, a nonionic water soluble polymer of 90,000 average-number molecular weight; a wall or overcoat comprising 95 wt% cellulose acetate possessing an acetyl content of 39.8% and 5 wt% polyethylene glycol of 3,350 number-average molecular weight; a 20 mil (0.50 mm) exit passageway; and an oxybutynin release rate of 0.295 mg per 1 hour over  
15 19.9 hours.

### **EXAMPLE 15**

A dosage form designed and shaped as a pharmaceutically acceptable  
20 tablet for the oral administration of a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salts was made by following the above examples. The dosage form provided by the example comprises a drug composition weighing 92 mg comprising 5.45 wt% of oxybutynin hydrochloride, 9.98 wt% of sodium chloride, 82.16 wt% of  
25 polyethylene oxide of 100,000 molecular weight, 2.00 wt% of hydroxypropylmethylcellulose of 11,300 molecular weight, 0.25 wt% of magnesium stearate, 0.08 wt% of butylated hydroxytoluene, and 0.05 wt% of green ferric oxide. The composition was surrounded by a wall comprising a semipermeable cellulose acetate polymer comprising a 39.8% acetyl content and  
30 polyethylene glycol comprising a 3,350 molecular weight. The dosage form

comprised can exit for delivering oxybutynin to the gastrointestinal tract of a patient.

#### **EXAMPLE 16**

5

A dosage form adapted as an orally administrable tablet was made according to the above examples. The dosage form of this example comprises a drug composition weighing 92 mg and comprising 5.45 wt% oxybutynin hydrochloride, 9.98 wt% sodium chloride, 82.19 wt% polyethylene oxide possessing a 200,000 molecular weight, 2.00 wt% hydroxypropyl-methylcellulose of 11,300 molecular weight, 0.25 wt% magnesium stearate, 0.08 wt% butylated hydroxytoluene, and 0.05 wt% green ferric oxide; a push composition initially in contact with the drug composition, weighing 62 mg and comprising 63.67 wt% polyethylene oxide possessing a 2,000,000 molecular weight, 30.00 wt% sodium chloride, 5.00 wt% hydroxypropylmethylcellulose of 11,200 molecular weight, 1.00 wt% of a 95.5 mixture of black iron oxide/lactose, 0.25 wt% magnesium stearate, and 0.08 wt% butylated hydroxytoluene; a wall weighing 19 mg that surrounds the compositions and comprises 99 wt% of cellulose acetate of 39.8% acetyl content, and 1.00 wt% polyethylene glycol of 3,350 molecular weight; a yellow color overcoat weighing 100 mg; and an exit in the wall for delivering the drug to a patient. The dosage form exhibited a cumulative release of oxybutynin hydrochloride of greater than zero mg to 1 mg in 0 to 4 hours, 1 mg to 2.5 mg in 0 to 8 hours, 2.75 mg to 4.25 mg in 0 to 14 hours, and 3.75 mg to 5 mg in 0 to 24 hours.

25

#### **EXAMPLE 17**

A dosage form for the oral administration of oxybutynin was made by following the above examples. The dosage form comprises a 92 mg drug composition comprising 10.90 wt% oxybutynin hydrochloride, 7.48 wt%

30

sodium chloride, 79.25 wt% polyethylene oxide possessing a 200,000 molecular weight, 1.99 wt% hydroxypropylmethylcellulose possessing a 11,300 molecular weight, 0.25 wt% magnesium stearate, 0.08 wt% butylated hydroxytoluene, and 0.05 wt% red ferric oxide; a push composition weighing  
5 62 mg and comprising 63.67 wt% polyethylene oxide possessing a 2,000,000 molecular weight, 30 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose possessing a 11,300 molecular weight, 1.00 wt% black iron oxide/lactose (95:5), 0.25 wt% magnesium stearate, and 0.08 wt% butylated hydroxytoluene; a wall that envelopes the compositions weighing 19 mg  
10 comprising 99 wt% cellulose acetate comprising a 39.8 acetyl content, and 1 wt% polyethylene glycol 3350; a exit in the wall; and a 10 mg push overcoat. The dosage form delivers in 0 to 4 hours up to 20% (up to 2 mg) of oxybutynin hydrochloride, in 0 to 8 hours 20 to 50% (2.0 to 5.0 mg) of oxybutynin salt; in 0 to 14 hours 50 to 85% (5.5 mg to 8.5 mg) of oxybutynin;  
15 and 0 to 24 hours greater than 75% (greater than 7.5 mg) of the drug.

#### **EXAMPLE 18**

A dosage form for the oral delivery of a member selected from the  
20 group consisting of oxybutynin and its pharmaceutically acceptable salts was made according to the above examples. The dosage form comprised a drug layer weighing 92 mg comprising 16.30 wt% oxybutynin chloride, 4.98 wt% sodium chloride, 76.35 wt% polyethylene oxide of 200,000 molecular weight, 1.99 wt% hydroxypropylmethylcellulose, 0.25 wt% magnesium stearate, 0.08  
25 wt% butylated hydroxytoluene, 0.02 wt% black iron oxide/lactose (95:5); a push composition weighing 62 mg comprising 63.67 wt% polyethylene oxide possessing a 2,000,000 molecular weight, 30.00 wt% sodium chloride, 5.00 hydroxypropylmethylcellulose of 11,300 molecular weight, 1.00 wt% black iron oxide/lactose (95:5), 0.25 wt% magnesium stearate, and 0.08 wt%  
30 butylated hydroxytoluene; a wall weighing 19 mg comprising a composition

permeable to fluid flux, impermeable to drug flux comprising 99.00 wt% cellulose acetate having a 39.8 acetyl content, and 1.00 wt% polyethylene glycol 3350; a passageway in the wall; and an overcoat weighing 10 mg colored grey. The dosage form exhibited a cumulative release rate of up to 3 mg in 0 to 4 hours; 3 mg to 7.5 mg in 0 to 8 hours; 8 mg to 13 mg in 0 to 14 hours; and 12 mg to 15 mg in 0 to 24 hours.

#### EXAMPLE 19

A dosage form was prepared according to the previous examples comprising an oxybutynin salt, that delivers up to 1.60 mg in 0 to 4 hours, up to 5 mg in 0 to 8 hours, up to 8.5 mg in 0 to 12 hours, up to 11 mg in 0 to 16 hours, and up to 15 mg in 0 to 24 hours.

#### EXAMPLE 20

A solid, orally administrable dosage form comprising 1 mg to 100 mg of a drug selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt is prepared by following the previous examples.

#### EXAMPLE 21

Dosage forms for administering oxybutynin were prepared according to the above examples, and the oxybutynin release rate profile are illustrated in Figures 1 and 2. Figure 1 depicts the cumulative amount of the dose released normalized to the percent of the dose released from dosage forms comprising 5 mg, 10 mg, and 15 mg of oxybutynin. Figure 2 depicts the average release rate expressed as percent of the total dose per hour for dosage forms comprising 5 mg, 10 mg, and 15 mg of oxybutynin.

EXAMPLE 22

A method of manufacturing a sustained release dosage form for managing oxybutynin and its desethylmetabolite in plasma, is provided, which method of manufacture comprises  
5 the incorporation of an effective amount of oxybutynin or its pharmaceutically acceptable salt in a sustained and controlled release dosage form which release oxybutynin continuously at a controlled zero order rate to provide a relatively higher oxybutynin concentration and a relatively  
10 lower desethylmetabolite concentration than provided by an immediate release dosage form profile.

EXAMPLE 23

The drug oxybutynin, identified as OXY, was administered in a clinical study to a number of patients to  
15 treat urinary incontinence. Patients who self-administered oxybutynin often quit or discontinue treatment due to its anti-cholinergic side effects, which appear to be peak-concentration related. The present invention thus provides a sustained release (SR) controlled-release (CR) oral  
20 dosage form comprising oxybutynin designed to provide both oxybutynin therapy throughout the entire gastrointestinal tract and a continuous plasma drug concentration that avoid peak and valley concentrations. The sustained release dosage form of this invention continuously delivers  
25 oxybutynin throughout the entire gastrointestinal tract (GI), thereby making it therapeutically effective for oxybutynin to be absorbed throughout the entire gastrointestinal tract into the blood. That is, the controlled-extended release dosage form of this invention  
30 maintains a therapeutic plasma concentration free of an overdose and free of an ineffective underdose of

oxybutynin.

In a multiple dose, crossover study, 13 healthy female volunteers of 41 to 68 years of age received either 5 mg of oxybutynin immediate release (IR) every 8 hours, or three 5 mg controlled release (CR) once a day, for four days. The patients blood was sampled on days 1 and 4 to quantify oxybutynin and its desethylmetabolite (DESOXY) by liquid chromatography mass spectroscopy (LC/MS). The oxybutynin was absorbed rapidly following immediate-release (IR) dosing with a mean  $C_{max}$  of 12 ng/ml.  $C_{max}$  is the maximum concentration after dosing in the plasma. The drug release kinetics for the controlled-release (CR) plasma concentration rose slowly, reaching a mean  $C_{max}$  value of 4.2-6.7 ng/ml. The metabolite DESOXY was formed rapidly following immediate release, and its formation paralleled the slow absorption of oxybutynin following controlled release. The DESOXY had a shorter  $t_{1/2}$  life compared to OXY, indicating presystemic metabolite formation assuming it to be true metabolite  $t_{1/2}$ . Single and multiple dose AUC values were similar for both the controlled release and the immediate release suggesting time invariant pharmacokinetics. AUC denotes the area under the plasma concentration profile. The 4 day OXY and DESOXY AUC and their ratios are presented in the Table below wherein BA denotes the percent bioavailable, that is, BA denotes the relative amount of oxybutynin absorbed from the controlled release (CR) dosage form compared to the immediate release (IR) dosage form, and  $C_{max}$  denotes the maximum concentration.



	OXY (AUC) (ng.h/mL)	DESOXY (AUC) (ng.h/mL)	OXY/DESOXY Ratio	OXY (BA%)	DESOXY (BA%)
IR	81	483	0.18		
CR	109	304	0.41	153	69

The higher ratio of OXY-BA following CR compared to IR suggests lower metabolic formation on first pass. This indicates CR could reach the colon within 3-5 hours post dosing. Presystemic cytochrome P450-mediated oxidation may occur in the upper part of the gastrointestinal tract; then, drug release from CR in the colon escapes presystemic metabolism, which could explain the higher OXY/DESOXY ratio and increased OXY BA following CR.

The dosage form and the oxybutynin composition of this invention, as seen from the above disclosure, can be used in a method for administering a drug by the oral route, or the dosage form and composition can be sized and shaped for administering a drug by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy, and they can be used when a smaller dose of drug is needed for immediate therapy. The latter routes can be used as a by-pass of the first pass of hepatic metabolism of the drug.

In summary, it will be appreciated that the present invention contributes to the art an unobvious dosage form that possesses practical utility, can administer a drug at a dose-metered release rate per unit time.

## CLAIMS:-

1. A controlled release dosage form comprising oxybutynin or a pharmaceutically acceptable biologically active salt thereof adapted to release oxybutynin or its salt at a biologically effective rate over time to an environment of use,

characterized in that the oxybutynin or active salt is adapted to be partially converted to its desethyl metabolite in the environment of use, and in that the rate of release of oxybutynin or salt thereof from the dosage form is adapted to provide a controlled release up to 30 hours to provide a higher oxybutynin/desethyl metabolite ratio than 0.18:1.

15

2. A dosage form according to claim 1 adapted such that the plasma levels of the desethyl metabolite does not exceed 350 ng.h/ml.

20 3. A dosage form according to either of claims 1 or 2 when the ratio is 0.25 to 0.45:1.

4. A dosage form according to claim 3 wherein the ratio is 0.35 to 0.41:1.

25

5. A controlled release dosage form comprising oxybutynin or a pharmaceutically acceptable biologically active salt thereof adapted to release the oxybutynin or salt thereof at a biologically effective rate over time to an environment of use;

characterized that the oxybutynin or salt thereof is

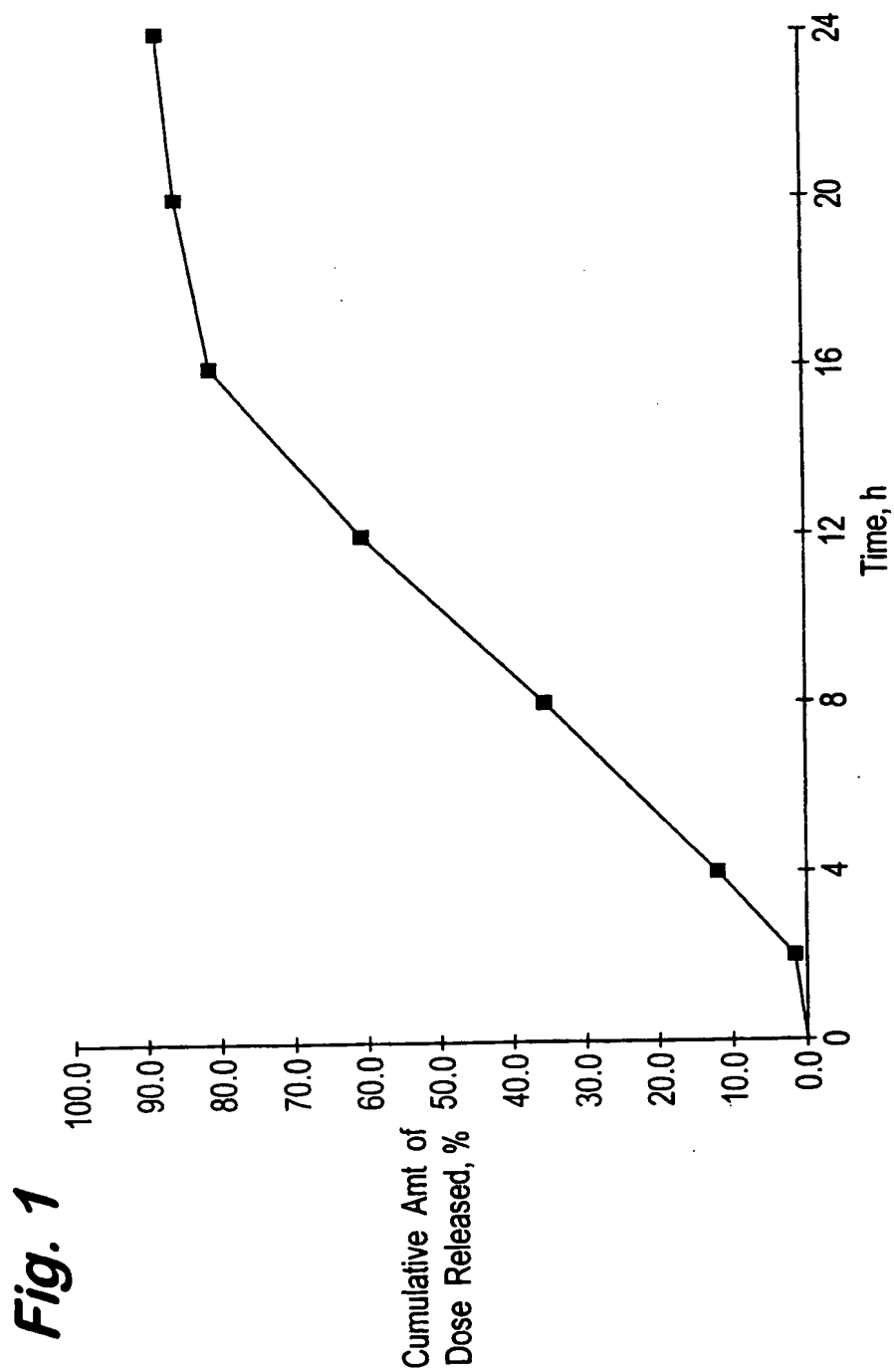
adapted to be partially converted to its desethylmetabolite in the environment of use and in that the rate of discharge of the oxybutynin and salt thereof from the dosage form is adapted to be controlled so that the plasma levels of the 5 desethylmetabolite do not exceed 350 ng.h/ml.

6. A dosage form according to any of claims 1 to 5 adapted for absorption throughout at least the majority of the length of the gastrointestinal tract.

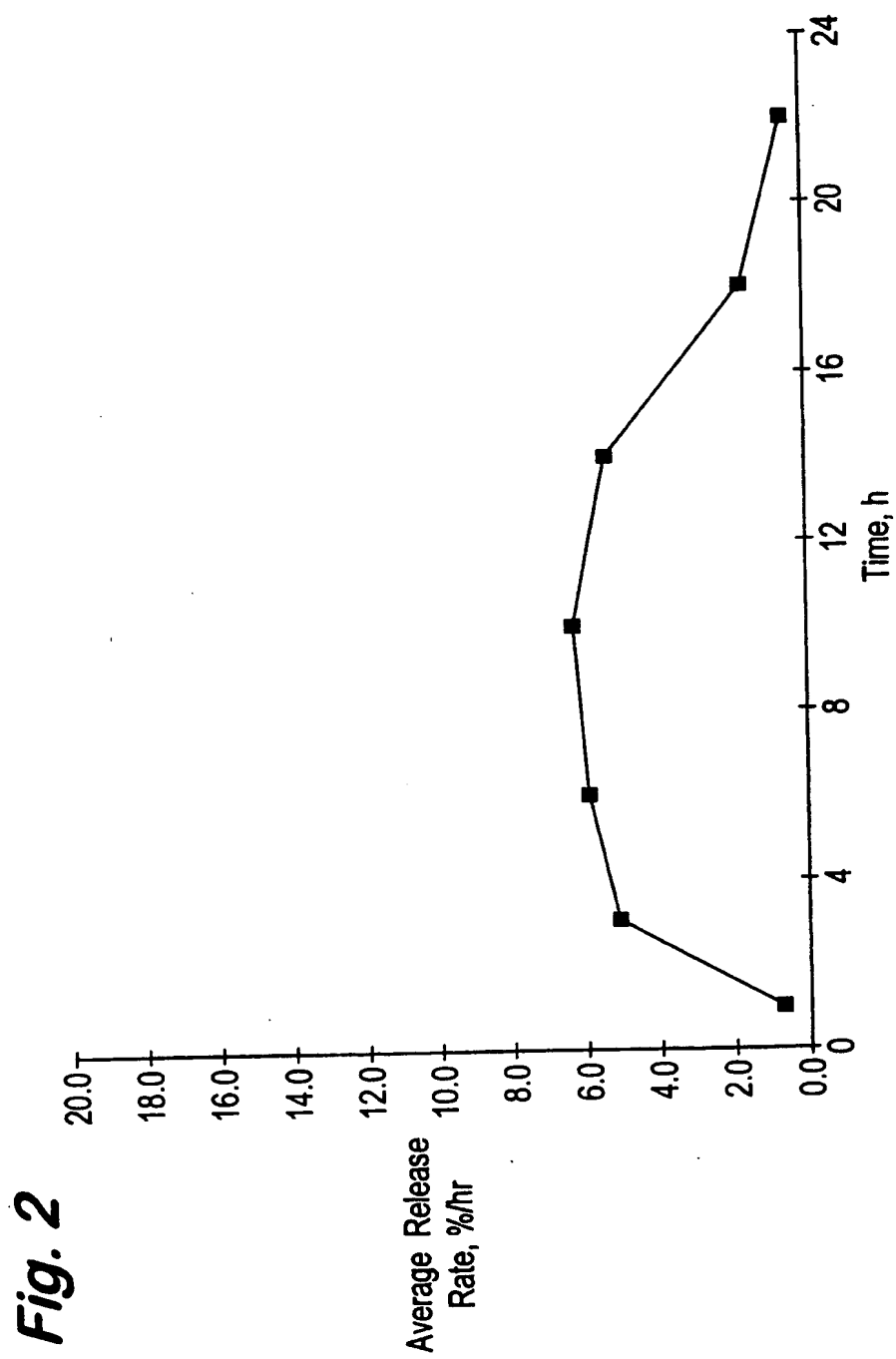
10

7. A dosage form according to any of claims 1 to 6 comprising 240 ng to 650 mg of oxybutynin or its pharmaceutically acceptable salt.

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2/2



# INTERNATIONAL SEARCH REPORT

In national Application No

PCT/IB 98/01982

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/215

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37202 A (ALZA CORP) 28 November 1996 see page 13 - page 18; examples 1-7 see claims	1-7
X	WO 96 12477 A (LEIRAS OY ;RANTALA PERTTI (FI)) 2 May 1996 "Results" see page 11 - page 12 see claims see figures	1-7
X	US 5 811 126 A (KRISHNAMURTHY THINNAYAM N) 22 September 1998 see column 12 - column 15; examples 11-19	1-7
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

14 April 1999

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Seegert, K

## INTERNATIONAL SEARCH REPORT

Int .tional Application No

PCT/IB 98/01982

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 9409  Derwent Publications Ltd., London, GB;  Class B05, AN 94-068306  XP002096606  &amp; JP 06 009388 A (KODAMA KK)  , 18 January 1994  see abstract</p> <p>----</p>	1-7
X	<p>DATABASE WPI  Section Ch, Week 9404  Derwent Publications Ltd., London, GB;  Class A96, AN 94-031722  XP002096607  &amp; JP 05 339151 A (KODAMA KK)  , 21 December 1993  see abstract</p> <p>----</p>	1-7
X	<p>GUPTA S.K. ET AL: "Evidence for  Site-Specific Presystemic Metabolism of  Oxybutynin Following Oral Administration"  CLINICAL PHARMACOLOGY &amp; THERAPEUTICS,  vol. 61, no. 2, 1997, page 227 XP002099744  see the whole document</p> <p>----</p>	1-7
X	<p>NILSSON C.G. ET AL: "Comparison of a  10-mg Controlled Release Oxybutynin Tablet  with a 5-mg Oxybutynin Tablet in Urge  Incontinent Patients"  NEUROLOGY AND URODYNAMICS,  vol. 16, no. 6, 1997, pages 533-542,  XP002099745  see page 539; figure 1  see page 540; table IV</p> <p>-----</p>	1-7

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No

PCT/IB 98/01982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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